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SESQUITERPENOIDS—II

THE CHEMISTRY OF SOME 7α(H)- AND 7β(H)-EUDESMAN-3,6-DIONES AND RELATED COMPOUNDS

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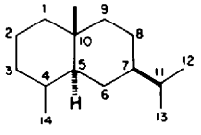
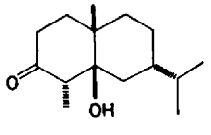
Abstract—The chemistry of some compounds related to (+)-6β-hydroxy-7β(H)-eudesm-4-en-3-one (IV) is described. The stereochemistry of the reduction products of both (+)-7β(H)-eudesm-4-en-3,6-dione (VI) and (+)-eudesm-4-en-3,6-dione (VIII) is established, and the equilibrium between these two ketones is discussed. Finally an attempt to prepare 6α-hydroxy-7β(H)-eudesm-4-en-3-one is mentioned.

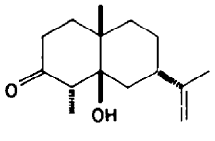
THE previous paper in this series[1] described the chemistry of some 7β(H)-eudesm-11-en-3,6-diones and related compounds. This paper, which represents a continuation of that work, alludes to the chemistry of some 7α(H)- and 7β(H)-eudesman-3,6-diones. In particular a convenient route to the diketone (−)-4β(H)-eudesman-3,6-dione (XV) is outlined. This diketone is quite important as a possible point of departure for the synthesis of sesquiterpenes in the eudesmane series which carry an oxygen function at position 6. (The nomenclature used in this paper is based as before upon the eudesmane (I) of known absolute stereochemistry.) It will be clear that the methods described in this paper cannot be used to prepare the remaining 7α(H)-eudesm-11-en-3,6-diones, since it is not possible to epimerize the corresponding 7β(H)-compounds and at the same time preserve the 11-ene system.[1]



I



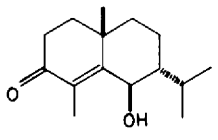
II



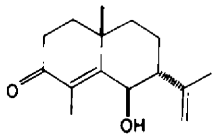
III

These investigations started with the preparation of (−)-5β-hydroxy-4β,7β(H)-eudesman-3-one (II) by the hydrogenation of the corresponding 11-ene (III).[2] The ketol (II) was smoothly converted by oxygen in the presence of sodium isopropoxide at 80° to (+)-6β-hydroxy-7β(H)-eudesm-4-en-3-one (IV).[3] A 6β-configuration for the hydroxyl group in this compound was originally suggested by Howe and McQuillin on stereochemical grounds,[3] and this was recently confirmed chemically for the corresponding 11-ene (V).[1]

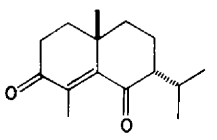
[1] D. W. Theobald, *Tetrahedron* **19**, 2261 (1963).
[2] R. Howe and F. J. McQuillin, *J. Chem. Soc.* 2670 (1956).
[3] H. M. E. Cardwell and F. J. McQuillin, *J. Chem. Soc.* 525 (1955); R. Howe and F. J. McQuillin, *Ibid.* 1513 (1958).



IV

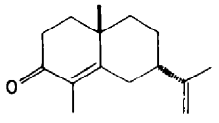


V

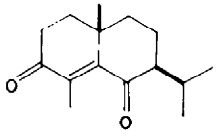


VI

The oxidation of the hydroxy-enone (IV) by chromic acid gave crystalline (+)-7β(H)-eudesm-4-en-3,6-dione (VI) in high yield. A comparison of the optical rotatory dispersion curve of this compound ($a = -32, +777$)* with those of the corresponding steroidal 4-en-3,6-diones[4] ($a = -90$) suggests that the 7α-isopropyl group probably causes some conformational abnormality in ring B. This is certainly not without precedent, for it is known that the rotatory dispersion curve of the ketone (VII) is unlike that of its 7α(H)-epimer.[4] And if conformational distortion is acknowledged in this compound (VII), then *a fortiori* it can be admitted in the ketone (VI) where ring B is a more flexible cyclohexanone system. The dispersion curves of the 7α(H)-ketone (VIII; $a = -105, +841$) and the corresponding steroids are, as expected, similar. The conformation of these ketones will be discussed further in considering their equilibration.

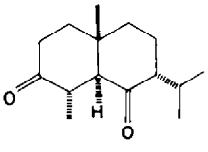


VII

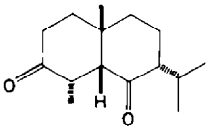


VIII

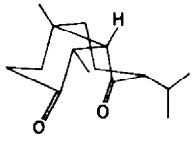
The hydroxy-enone (IV) resisted isomerization even under comparatively vigorous conditions (hot 50% aq H_2SO_4) which would certainly isomerize its steroidal analogues to 3,6-diones.[5] However reduction of (+)-7β(H)-eudesm-4-en-3,6-dione (VI) with zinc dust in acetic acid gave two diketones, IX, m.p. 114–115°, and X, m.p. 109°. These two diketones were identified as (+)-4β,7β(H)-eudesman-3,6-dione and (−)-4β,5β,7β(H)-eudesman-3,6-dione respectively, since they were also obtained by hydrogenating the corresponding 11-enes whose stereochemistry had already been established.[1] Further the diketone (IX) had previously been prepared by oxidizing



IX



X



XI

* a is defined as the difference between the molecular rotation, $[\phi]_L$, at the extremum of longer wavelength *minus* the molecular rotation, $[\phi]_S$, at the extremum of shorter wavelength divided by 100. Where two values of a are quoted, the first refers to the wavelength range 300–400 mμ and the second to the range 200–300 mμ.

[4] C. Djerassi, R. Riniker and B. Riniker, *J. Amer. Chem. Soc.* **78**, 6377 (1956).

[5] L. F. Fieser and M. Fieser, *Steroids* p. 202. Reinhold, New York (1959).

(+)-6β-hydroxy-4β,7β(H)-eudesman-3-one obtained in the lithium–ethylamine reduction of (+)-6β-hydroxy-7β(H)-eudesma-4,11-dien-3-one (V), with chromic acid at 0°.[1] The UV and IR spectra of the diketones (IX and X) were in no way remarkable. Perhaps this is surprising since the diketone (X) undoubtedly prefers the non-steroidal conformation (XI) in which the carbonyl groups lie fairly close to one another in almost the same plane.

Howe and McQuillin described the isomerization of the diketone (VI) into its 7α(H)-epimer (VIII) in cold ethanolic potassium hydroxide solution.[3] Further investigation of this reaction has now shown that there is an equilibrium between these two ketones. At 25°, the equilibrium mixture was found to contain 16 ± 2% of the ketone (VI). This leads to $\Delta G_{298} = -1{\cdot}1$ kcals/mole as a mean value for the free energy change for the reaction (VI) → (VIII). The composition of the equilibrium mixture was estimated both by direct chromatographic isolation of the pure components (total recovery from the reaction mixture was almost quantitative) and from a comparison of the optical rotations of equilibrium mixtures and the pure components.

Allinger and Hu determined the conformational preference of the isopropyl group by equilibrating *cis* and *trans* 1,3-diisopropylcyclohexane on palladium at high temperatures.[6] They found $\Delta G_{298} = -2{\cdot}10$ kcal/mole for the epimerization $Pr_{ax}^{i} \rightarrow Pr_{eq}^{i}$. This value might be expected to be less in a 2-isopropylcyclohexanone,[7] and this was indeed confirmed by Allinger and Blatter in a study of the equilibrium between *cis* and *trans* 2-isopropyl-4-t-butylcyclohexanone,[8] and later by Rickborn in an investigation of the equilibrium between *cis* and *trans* 1,2-diisopropylcyclohexanone.[9] There seems general agreement that in such a situation ΔG for the epimerization $Pr_{ax}^{i} \rightarrow Pr_{eq}^{i}$ is approximately −0·6 kcal/mole. As Allinger points out, it is clear from this that it is no longer valid to assume *a priori* that isopropyl groups in cyclohexanones are exclusively equatorial.

The rather high value of ΔG for the reaction (VI) → (VIII) clearly requires some explanation. Models allow three possible conformations, (XII, XIII and XIV) for the ring system of these compounds. Ring B in two of these, (XII and XIII), is boat-like, while in XIV it is chair-like. It is reasonable to suppose that ring B is encouraged to assume these conformations, since by so doing, some relief in the steric compression between the otherwise coplanar $C_{(4)}$—methyl and $C_{(6)}$=oxygen can be achieved. In conformation XII however, a 7β-configuration for the isopropyl group would be considerably destabilized by interaction with the $C_{(10)}$—methyl group. Strong repulsion between the $C_{(4)}$—methyl group and the $C_{(6)}$=oxygen would exacerbate this situation, as shown by the arrows in XII. Clearly this cannot be reconciled with the measured value of ΔG. In conformation XIII the isopropyl group would not be expected to show marked conformational preference, for models show that the environment of this group is practically the same whether it has a 7α- or a 7β-configuration. And strong repulsion between the $C_{(4)}$—methyl group and the $C_{(6)}$= oxygen would not have the effect of substantially destabilizing a 7α-isopropyl group, as shown by the arrows in XIII. However $C_{(7)}$ in conformation XIV with the chair-like

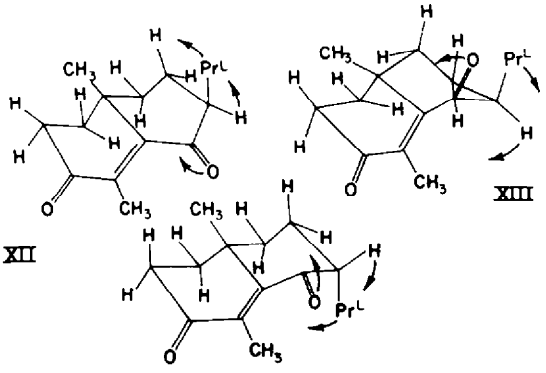
[6] N. L. Allinger and S. Hu, *J. Org. Chem.* **27**, 3417 (1962); cf. D. S. Noyce and L. J. Dolby, *Ibid.* **26**, 3619 (1961).

[7] W. Klyne, *Experentia* **12**, 119 (1956).

[8] N. L. Allinger and H. M. Blatter, *J. Amer. Chem. Soc.* **83**, 994 (1961).

[9] B. Rickborn, *J. Amer. Chem. Soc.* **84**, 2414 (1962).

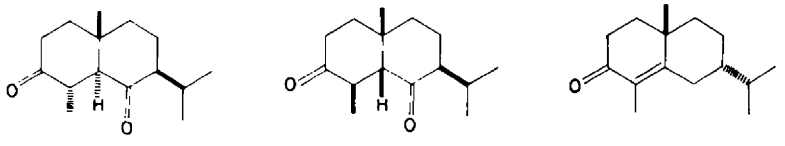
ring B carries almost pure axial and equatorial bonds. Strong repulsion between the $C_{(4)}$—methyl group and the $C_{(6)}$=oxygen may well cause the orientation of the 7α-isopropyl group to change in the direction shown by the arrows in XIV. If this is so, then the measured value of ΔG for the reaction (VI) → (VIII), which is larger than normal for the epimerization of 2-isopropylcyclohexanones, is explained. In fact a value lying somewhere between −0·6 and −2·1 kcal/mole would be expected. If this explanation is valid, then it is not surprising that the rotatory dispersion curve of the ketone VI is unlike that of steroidal 4-en-3,6-diones, whereas that of the ketone VIII is similar. For it is clear that the ketone VIII is not subject to the conformational stresses present in VI.



XII XIII

XIV

The reduction of the ketone (VIII) with zinc in acetic acid yielded only a single crystalline diketone identified as (−)-4β(H)-eudesman-3,6-dione (XV), m.p. 46–47°. The stereochemistry of this product was suggested by its rotatory dispersion curve ($a = -86$) which closely resembled that of the steroid analogue ($a = -67$).[4,10] It is surprising that no compound which could be characterized as 4α,5β(H)-eudesman-3,6-dione (XVI) was isolated. The 5α(H)-compound would be expected to be the major product of reduction in the 7α(H)-series, just as in the 7β(H)-series the 5β(H)-compound would be expected to predominate. It is a question of the most favourable conformation which will accommodate an equatorial isopropyl group. The diketone

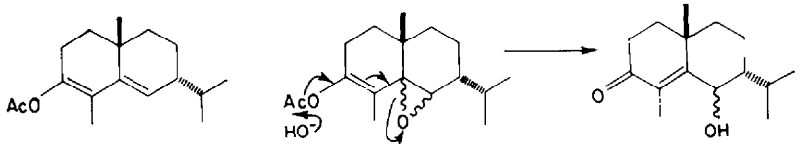


XV XVI XVII

(XV) was recovered unchanged from methanolic potassium hydroxide solution, and the diketones (IX and X) were both smoothly isomerized by the same reagent to the diketone (XV). These facts confirm the stereochemistry (XV). The potential synthetic importance of this ketone has already been mentioned.

[10] S. Julia, B. Decouvelaere, J-P. Lavaux, C. Moutonnier and P. Simon, *Bull. Soc. Chim. Fr.* 1223 (1963).

The oxidation of the ketol (II) with oxygen in the presence of sodium isopropoxide gives the 6β-hydroxy-enone (IV) in high yield. The corresponding 6α-hydroxy compound was not detected in the reaction product. A recently reported method for preparing both 6α- and 6β-hydroxy-4-en-3-ones in the steroid series[11] was used in an attempt to prepare 6α-hydroxy-7β(H)-eudesm-4-en-3-one. The enol-acetate (XVII)



XVIII XIX

was prepared from (+)-7β(H)-eudesm-4-en-3-one (XVII) and treated with perbenzoic acid in ether. The product was then warmed to 60° in methanolic potassium hydroxide solution (XIX) and the recovered material chromatographed. A 50–60% yield of the 6β-hydroxy compound (IV) was regularly realised, but no material which could be characterized as the 6α-epimer was isolated.

EXPERIMENTAL

M.ps are uncorrected. Specific rotations were determined for chloroform solutions at room temp. UV spectra were measured for ethanol solutions on a Unicam SP 700. IR spectra were measured with Perkin–Elmer spectrophotometers PE-21 and Infracord 137 with NaCl prisms. RD (rotatory dispersion) measurements were made in the laboratories of Professor W. Klyne, Westfield College, University of London.

Alumina used for chromatography refers to Peter Spence's Grade H, deactivated with 5% of 10% acetic acid. Petroleum ether refers to the fraction, b.p. 60–80°, unless otherwise stated.

(−)-*5β-Hydroxy-4β,7β(H)-eudesman-3-one* (II). (−)-5β-Hydroxy-4β,7β(H)-eudesm-11-en-3-one (III) in ethanol with platinum took up 1 mole hydrogen to give (−)-5β-hydroxy-4β,7β(H)-eudesman-3-one (II) which crystallized from pet. ether (b.p. 40–60°) as prisms, m.p. 64–66°; $[\alpha]_D$ −52° (*c*, 1·6). IR spectrum (in Nujol): ν_{max} 3500, 1710, 1375, 1355 cm^{-1}. Lit. records:[3] m.p. 64–65°; $[\alpha]_{5461}$ −57° (*c*, 3·8).

The *semicarbazone* crystallized from ethanol aq as needles, m.p. 248–250° (dec). (Found: C, 65·0; H, 9·5; N, 14·4. $C_{16}H_{29}N_3O_2$ requires: C, 65·1; H, 9·8; N, 14·3%).

(+)-*6β-Hydroxy-7β(H)-eudesm-4-en-3-one* (IV). This compound was prepared in the way described by Howe and McQuillin.[3] It was crystallized from pet. ether (b.p. 40–60°) as prisms, m.p. 91°; $[\alpha]_D$ +24° (*c*, 2·9). IR spectrum (in Nujol): ν_{max} 3500, 1655, 1610, 1375, 1355 cm^{-1}. Lit. records:[3] m.p. 90–91°; $[\alpha]_{5461}$ +27·2° (*c*, 3·5).

The *semicarbazone* crystallized from ethanol aq as plates, m.p. 212–214°. (Found: C, 65·8; H, 9·4; N, 14·0. $C_{16}H_{27}N_3O_2$ requires: C, 65·5; H, 9·2; N, 14·3%).

(+)-*7β(H)-Eudesm-4-en-3,6-dione* (VI). (+)-6β-Hydroxy-7β(H)-eudesm-4-en-3-one (IV; 300 mg) in purified acetone (15 ml) was treated with 8 N chromic acid aq at 0° until an orange colour persisted. After 2 min, the product was recovered by dilution with water and isolation in ether. (+)-7β(H)-Eudesm-4-en-3,6-dione (VI) was obtained as needles (from pet. ether at 0°), m.p. 79–80°; $[\alpha]_D$ +285° (*c*, 0·4). IR spectrum (in Nujol): ν_{max} 1660, 1385, 1365, 1230, 1205, 940 cm^{-1}. RD in methanol (*c*, 0·5): $[\phi]_{408}$ +1760°, $[\phi]_{377}$ +1490°, $[\phi]_{308}$ +5710°, $[\phi]_{279}$ +17600°, $[\phi]_{266}$ +25600°, $[\phi]_{261}$ +25100°, $[\phi]_{251}$ −38400°, $[\phi]_{315}$ −52100°, $[\phi]_{311}$ −42500°!* Lit. records:[3] m.p. 80°; $[\alpha]_{5461}$ +304° (*c*, 2·5).

The mono-2,4-dinitrophenylhydrazone crystallized from ethanol as orange needles m.p. 210°. Lit. records:[3] m.p. 208–209°.

Zinc–acetic acid reduction of (+)-7β(H)-*eudesm-4-en-3,6-dione* (VI). A solution of (+)-7β(H)-eudesm-4-en-3,6-dione (VI; 200 mg) in acetic acid (7 ml) was kept at 90° and zinc dust (1·5 g)

* ! means that measurements could not be made at lower wavelengths.

[11] J. P. Dusza, J. P. Joseph and S. Bernstein, *J. Org. Chem.* **27**, 4046 (1962).

added in small portions during 2 hr. The mixture was constantly agitated during this period. The solids were removed by filtration, and the product isolated by diluting the filtrate with water and extracting with ether. The product was obtained as a gum (180 mg) and was adsorbed on alumina (30 g).

Pet. ether–benzene (1:1) eluted (+)-4β,7β(H)-eudesman-3,6-dione (IX; 40 mg), which crystallized from pet. ether at 0° as prisms, m.p. 114–115°; $[\alpha]_D$ +151° (*c*, 2·2). IR spectrum (in Nujol): ν_{max} 1705, 1380, 1360, cm^{-1}. UV spectrum: λ_{max} 298 mμ (ε = 110). Lit. records:[1] m.p. 113–114°; $[\alpha]_D$ +156° (*c*, 1·7).

The *mono*-2,4-*dinitrophenylhydrazone* crystallized from chloroform–ethanol as yellow needles, m.p. 250–252°. (Found: C, 60·3; H, 6·5; N, 13·2. $C_{21}H_{28}N_4O_5$ requires: C, 60·6; H, 6·7; N, 13·5%).

Benzene eluted (−)-4β,5β,7β(H)-*eudesman*-3,6-*dione* (X) (110 mg), which crystallized from pet. ether as prisms, m.p. 109°; $[\alpha]_D$ −12° (*c*, 4·2). IR spectrum (in Nujol): ν_{max} 1705, 1375, 1355 cm^{-1}. UV spectrum: λ_{max} 296 mμ (ε = 120). (Found: C, 76·1; H, 9·9. $C_{15}H_{24}O_2$ requires: C, 76·3; H, 10·2%).

The *mono*-2,4-*dinitrophenylhydrazone* crystallized from ethanol as orange-yellow needles, m.p. 214–215°. (Found: C, 60·2; H, 6·6; N, 13·4. $C_{21}H_{28}N_4O_5$ requires: C, 60·6; H, 6·7; N, 13·5%).

The diketones (IX and X) were also prepared by the hydrogenation on platimum in ethanol of (+)-4β,7β(H)-eudesm-11-en-3,6-dione and (−)-4β,5β,7β(H)-eudesm-11-en-3,6-dione respectively of proven stereochemistry.[1]

The isomerization of (+)-7β(H)-*eudesm*-4-*en*-3,6-*dione* (VI). A solution of (+)-7β(H)-eudesm-4-en-3,6-dione (VI; 500 mg) and KOH (2·0 g) in ethanol (30 ml) and water (4 ml) was maintained at 25° under N_2 in the dark for 48 hr. Dilution with water and extraction with ether gave a nearly colourless oil (480 mg), n_D^{21} 1·5151; $[\alpha]_D$ +151° (*c*, 2·0).

This was adsorbed on alumina (70 g). Elution with pet. ether–benzene (5:3) gave (+)-*eudesm*-4-*en*-3,6-*dione* (VIII) as an oil (400 mg), b.p. 95–100°/0·2 mm (bath): n_D^{22} 1·5132; $[\alpha]_D$ +123° (*c*, 4·0). IR spectrum (natural film): ν_{max} 1705, 1380, 1360, 1190, 940 cm^{-1}. UV spectrum λ_{max} 254 mμ (ε = 12200). RD in methanol (*c*, 0·5): $[\phi]_{500}$ +370°, $[\phi]_{417}$ +605°, $[\phi]_{377}$ −35°, $[\phi]_{333}$ +4450°, $[\phi]_{305}$ +6100°, $[\phi]_{303}$ +10500°, $[\phi]_{274}$ +22900°, $[\phi]_{266}$ +28700°, $[\phi]_{250}$ 0°, $[\phi]_{233}$ −45000°, $[\phi]_{227}$ −42300°, $[\phi]_{217}$ −55400°, $[\phi]_{213}$ −44500! (Found: C, 76·6 H, 9·4. $C_{15}H_{22}O_2$ requires: C, 76·9; H, 9·4%).

The *mono*-2,4-*dinitrophenylhydrazone* crystallized from ethanol–chloroform as orange needles, m.p. 230–232°: (Found: C, 60·6; H, 6·0; N, 13·1. $C_{21}H_{26}N_4O_5$ requires: C, 60·9; H, 6·3; N, 13·5%).

Lit. records[3] properties for this ketone (VIII) which are probably those of an equilibrium mixture.

Elution with pet. ether–benzene (10:7) gave (+)-7β(H)-eudesm-4-en-3,6-dione (VI; 70 mg), m.p. 77–79°.

A number of estimations of the composition of the equilibrium mixture at 25° in ethanol containing catalytic quantities of KOH (1% of the weight of the ketone) by rotation measurements and chromatography led to a value of 16 ± 2% for the proportion of the ketone (VI) present at equilibrium.

Zinc–acetic acid reduction of (+)-*eudesm*-4-*en*-3,6-*dione* (VIII). (+)-Eudesm-4-en-3,6-dione (VIII; 500 mg) in acetic acid (15 ml) at 90° was treated with zinc dust (3 g) in small portions during 1·5 hr. Recovery in the usual way gave an oil (480 mg), which was adsorbed on alumina (60 g).

Pet. ether–benzene (1:1) eluted (−)-4β(H)-*eudesman*-3,6-*dione* (XV) (390 mg), which crystallized from pet. ether at 0° as prisms, m.p. 46–47°; $[\alpha]_D$ −17° (*c*, 3·0). IR spectrum (in Nujol): ν_{max} 1705, 1375, 1355 cm^{-1}. UV spectrum: λ_{max} 298 mμ (ε = 90). RD in methanol (*c*, 0·5): $[\phi]_{400}$ −401°, $[\phi]_{318}$ −3920°, $[\phi]_{275}$ +4770°, $[\phi]_{250}$ +3630°, $[\phi]_{244}$ +3660°, $[\phi]_{223}$ +6180°! (Found: C, 76·0; H, 10·0. $C_{15}H_{24}O_2$ requires: C, 76·3; H, 10·2%).

The *mono*-2,4-*dinitrophenylhydrazone* crystallized from ethanol as yellow needles, m.p. 189–190°. (Found: C, 60·5; H, 6·7; N, 13·1. $C_{21}H_{28}N_4O_5$ requires: C, 60·6; H, 6·7; N, 13·5%).

Elution with solvents of increasing polarity yielded small quantities of oily material which could not be characterized.

The isomerization of the diketones (IX, X *and* XV). The diketone (XV) was recoverd unchanged from solution in 0·4 N methanolic KOH. This diketone was also isolated from solutions of the diketones (IX and X) in the same reagent.

The enol–acetylation of (+)-7β(H)-*eudesm*-4-*en*-3-*one* (XVII). A solution of the ketone (XVII;

750 mg) in isopropenyl acetate (30 ml) containing toluene-*p*-sulphonic acid (120 mg) was heated under reflux for 7 hr. Solid $NaHCO_3$ was added to the cooled solution, and the product isolated in ether. Removal of the solvents left a pale yellow oil (700 mg), which was adsorbed on alumina (30 g).

Elution with pet. ether gave (+)-3-*acetoxy*-7β(H)-*eudesma*-3,5-*diene* (XVIII) (420 mg) as an oil, b.p. 110–115°/0·2 mm (bath); n_D^{19} 1·5090; $[\alpha]_D$ +83° (*c*, 3·0). IR spectrum (natural film): ν_{max} 1755, 1720, 1220, 1080 cm^{-1}. UV spectrum: λ_{max} 240 mμ (ε = 16200). (Found: C, 77·5; H, 9·7. $C_{17}H_{26}O_2$ requires: C, 77·9; H, 9·9%).

Elution with pet. ether–benzene (3:1) yielded unchanged starting material.

Attempted preparation of 6α-*hydroxy*-7β(H)-*eudesm*-4-*en*-3-*one*. The enol-acetate (XVIII; 260 mg) in ether (15 ml) was treated with a solution of perbenzoic acid (160 mg) in ether (10 ml), and the mixture set aside in the dark at 20° for 48 hr. Removal of the ether left a gum which was kept at 60° under nitrogen for 2 hr in ethanol (10 ml) containing KOH (0·5 g). Isolation in ether gave an oily product (220 mg), which was adsorbed on alumina (20 g).

Elution with benzene–ether (20:1) gave (+)-6β-hydroxy-7β(H)-eudesm-4-en-3-one (IV) (140 mg), which crystallized from pet. ether (b.p. 40–60°) as prisms, m.p. 90–91°.

Elution with solvents of increasing polarity gave small quantities of gums none of which could be characterized as the 6α-hydroxy compound.

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